One Year Post Exclusivity Adverse Event Review: Glyburide-Metformin

Pediatric Advisory Committee Meeting
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Background Drug Information

- **Drug:** Glucovance® (glyburide-metformin)
- **Therapeutic Category:** antihyperglycemic
- **Sponsor:** Bristol-Myers Squibb Company
- **Indications:**
  - Adjunct treatment for Type II Diabetes Mellitus (DM) with diet and exercise
  - Second line for Type II DM if metformin or sulfonylurea fail
- **Original Market Approval:** July 31, 2000
- **Pediatric Exclusivity Granted:** October 8, 2003

Background Drug Information

- **Adult and Adolescent Dosage:**
  - Initial: 1.25/250 mg titrated to control glucose levels
  - Second line: 2.5/500 mg or 5.0/500 mg BID
- **Mechanism of action:**
  - Glyburide: stimulates release of insulin
  - Metformin: improves glucose tolerance

Drug Use Trends in Outpatient Settings: Glyburide-Metformin

- Total prescriptions for oral antihyperglycemic products have increased from 97 million (Nov 2001- Oct 2002) to 107 million (Nov 2003- October 2004).[1]
- Glucovance and its generic combination product accounted for 6.8 million prescriptions, almost 70% of the combination product market share (Nov 2003-Oct 2004).[1]
- Pediatric participants accounted for .06% of the claims for oral antihyperglycemic products. The number of claims was too small to estimate the number of prescriptions dispensed for pediatrics (Nov 2001- Oct 2004).[2]

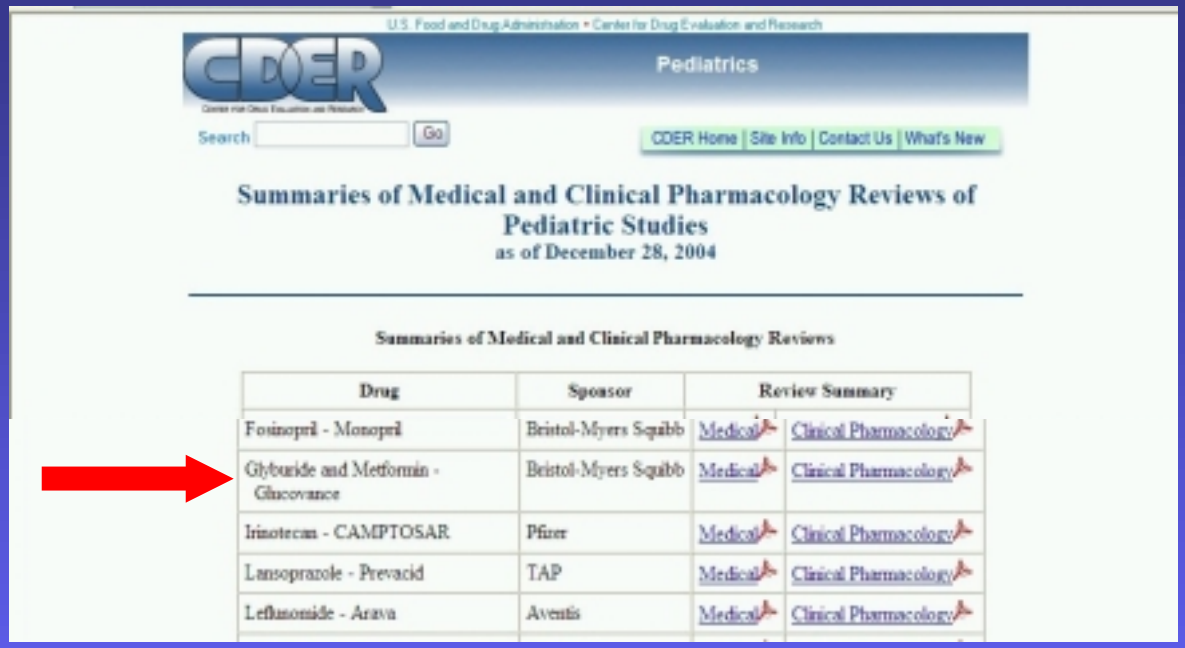
[1]IMS Health, National Prescription Audit *Plus*™, Nov 2001 – Oct 2004, Data Extracted Nov 2004
[2]Caremark Dimension Rx™, Inc, Nov 2001 – Oct 2004, Data extracted Nov 2004

Drug Use Trends in Outpatient Settings: Glyburide-Metformin

- Prescribers (Nov 2003 to Oct 2004)[1]
  - Internists and family practitioners accounted for 66% of the prescriptions written.
  - Pediatricians wrote <1%.
- Diagnosis[2]
  - Adults: diabetes without complications
  - Pediatric indications could not be analyzed during sampling period due to sparse data.

[1]IMS Health, National Prescription Audit *Plus*™, Nov 2001 – Oct 2004, Data Extracted Nov 2004
[2]IMS Health, National Disease and Therapeutic Index™, Nov 2001 – Oct 2004, Data Extracted Nov 2004

- http://www.fda.gov/cder/pediatric/Summaryreview.htm



Pediatric Exclusivity Studies: Glyburide-Metformin

- Indication: Type II Diabetes Mellitus
- Studies performed:
  - PK and safety study
  - 26 week efficacy and safety study

Pediatric Exclusivity Studies: PK

- Single dose PK study in Type II DM (age 11-16 years, n=28)
- PK not significantly different from adults
- Glyburide and metformin pharmacokinetics comparable between children and adolescent patients
- No apparent relationship of age or BSA on dose (limited data)

Pediatric Exclusivity Studies: Safety and Efficacy

- Active, double-blind controlled 26 week trial of adolescent patients with type II DM (age 9-16, n=167)
- 3 arms: glyburide/metformin (1.25/250 mg), glyburide (2.5 mg), and metformin (500 mg) titrated for glucose control
- Primary efficacy: change in HgbA1c
- Glucovance not statistically superior to either metformin or glyburide alone

Pediatric Exclusivity Studies: Safety Findings

- Drug specific safety concerns: diarrhea, GI discomfort, hypoglycemia
- No patient experienced serious adverse event, marked laboratory abnormality or discontinued prematurely due to an adverse event.
- No unexpected safety findings
- Due to dose sparing of metformin, patients on Glucovance appeared to have fewer GI complaints than metformin.
- Hypoglycemia appeared related to glyburide dose

Labeling Changes Resulting from Exclusivity Studies

- Clinical trial data included in Pediatric Use section
  - "the safety and efficacy of Glucovance were evaluated in an active controlled, double blind, 26 week trial involving a total of 167 pediatric patients with type 2 diabetes……
  - "Glucovance was not shown statistically to be superior to either metformin or glyburide with respect to reducing HgbA1c."
- The statement "Glucovance is not recommended for pediatric patients" removed from label

Relevant Safety Labeling

- Pregnancy Category B
- Contraindications: renal dysfunction, congestive heart failure, acute metabolic acidosis
- Boxed warning: lactic acidosis
- Special warning: increased cardiovascular mortality compared with diet +/- insulin

Adverse Event Reports since Market Approval: Glyburide-Metformin
07/31/00 - 11/08/04

- Total number of reports, all ages[†*]:
  - 480 reports (476 US)
    - 35 serious (31 US)
      - 4 deaths (4 US)
- Pediatric reports: 0

[†]Includes reports with unknown age

[*]Counts may include duplicate reports

Adverse Event Reports during the One-Year Post-Exclusivity Period: Glyburide-Metformin
10/08/03 - 11/08/04

- Total number of reports, all ages[†*]:
  - 171 reports (168 US)
    - 13 serious (10 US)
      - 0 deaths
- Pediatric reports: 0

[†]Includes reports with unknown age

[*]Counts may include duplicate reports

Top 20 Adverse Events during the One-Year Post-Exclusivity Period: (Adults: n=161)

Labeled

Diarrhea

Hypoglycemia

Nausea

Dizziness

Stomach discomfort

Unlabeled

Blood glucose increased

Blood glucose decreased

Constipation

Asthenia

Tremor

Weight increased

Fatigue

Hyperhidrosis

Blood glucose fluctuation

Dyspepsia

Abdominal pain upper

Flatulence

Weight decreased

Feeling abnormal

Feeling hot

Summary: Glyburide-Metformin

- Minimal use in pediatric patients
- No pediatric adverse events
- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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